



IN THE UNITED STATES PATENT OFFICE

Application Serial No. 08/352,697

Our Ref: PT-1038

Applicants:

Rudolf E. Falk
Samuel S. Asculai
Ehud Shmuel Klein
David W. Harper
David Hochman
and Don Purschke

Title:

FORMULATIONS CONTAINING
HYALURONIC ACID

Examiner:

Elli Peselev

Group Art Unit: 1211

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia
U.S.A. 22202

DECLARATION OF EVA TURLEY
under § 1.132

I, EVA TURLEY, make oath and say as follows:

1. I am the same Eva Turley whose Declaration dated August, 1996, was filed in the prosecution of the above-identified application. This declaration is referred to Application Serial No. 07/675,908.

2. THE OFFICE ACTION

For the purposes of preparing this Declaration, I was asked to review the Official Action Summary issued by the Patent Office, mailed December 19, 1996,

#9
9/10/97

and particularly the objections based on the prior art (specifically U.S. Patent No. 4,736,024 (Della Valle et al)).

3. I understand from the action that, according to Examiner Peselev, Della Valle is purported to have taught the use of his ophthalmic composition in dermatology and thus greater amounts would be contemplated to be used and that the relative amounts of the components in Applicants' composition are not particularly critical. I also understand that according to Examiner Peselev the combinations of actives and hyaluronan taught in Della Valle read in light of the concentrations given at column 9 of United States Patent 4,736,024 of between 0.01% and 75% for each of the two components is purported to teach the invention claimed by Applicants.

4. As an expert in hyaluronan, at the time of this invention, persons skilled in the art would, when applying hyaluronic acid topically on the skin, have expected it to **dry up and flake off**, whatever the areas of the skin to which it was applied. If applied elsewhere, such as on mucous membranes such as the mouth, it would have been expected to become **diluted and be washed away** by the wetness (for example saliva) found on the mucous membranes.

5. This is consistent with all the teachings of the publications both prior to Della Valle (U.S. Patent 4,736,024) and subsequent to same before the filing of PCT Application WO 91/04058 which entered the National Phase in the United States under Application Serial No. 07/675,908 (by Falk and Asculai).

6. Exemplary of these teachings are United States Patent 4,808,576 (Schultz), the articles entitled "Hyaluronic Acid, Its Structure and Use", "Polymers", in Cosmetics and Toiletries, Vol. 99, June 1984, and "Effect of Several Penetration

Enhancers on the Percutaneous Absorption of Indomethacin in Hairless Rats", Chem. Pharm. Bull. 36(4), 1519-1528 (1988).

Schultz (U.S. Patent 4,808,576) taught at column 6, lines 1-9:

"Without the transdermal carrier the sodium hyaluronate applied was ineffective."

Of importance is the statement at column 12, lines 14-18:

"The hyaluronate solution simply evaporated to dryness leaving a film on the skin of the subject."

In the article found in "Polymers", in Cosmetics and Toiletries, Vol. 99, June 1984, entitled "Hyaluronic Acid, Its Structure and Use", at page 71 Balazs et al (the same Balazs in U.S. Patent 4,141,973) state:

"The stratum corneum is known to be impermeable to molecules as large as hyaluronic acid."

"Therefore, it is not expected that even very short chains of oligosaccharides of degraded hyaluronic acid that contain more than 5 to 10 pentisaccharide units can pass through this layer of the skin. There is no evidence in the literature that any hyaluronic acid - in any solvent or with any added carrier - will penetrate deeper than the crevices between the desquamating cells."

In an article entitled "Effect of Several Penetration Enhancers on the Percutaneous Absorption of Indomethacin in Hairless Rats", Chem. Pharm. Bull.

36(4), 1519-1528 (1988) there is a discussion of the effect of several penetration enhancers on the percutaneous absorption of drugs. Note the use of the expression "percutaneous absorption". In other words the medicine is absorbed through the skin and the penetration enhancers enable such absorption. One of the compounds tested is sodium hyaluronate and the clinicians found that it had no enhancing effect on the skin permeation of indomethacin.

7. The prior art teaches the fact that there is no penetration by any formulation in the prior art (see United States Patents 4,141,973 and 4,711,780).

8. It was my experience at the time that persons skilled in the art at that time thought it "trendy" to put hyaluronic acid into products in small amounts (it was non-toxic). These small amounts were expected by such persons to do what was known (before drying up). In such small amounts, the hyaluronic acid could only do what was known - provide a retard effect by releasing the medicine slowly as was taught in United States Patent 4,141,973 at column 14, lines 31-36.

"...the HUA of the invention can be used as a vehicle for any kind of intraarticular medication to protect the articular cartilage from the possible harmful effects of the particular drug used, and to prolong the effect of the drug by decreasing its diffusion out of the articular space."

9. This brings me now to Della Valle, United States Patent 4,736,024 (claiming priority from 1985 application filed in Italy). Della Valle teaches specifically at column 1, lines 46-53 that

"When the medicaments are administered in the form of concentrated solutions with elastic-viscose characteristics or in solid

form, it is possible to obtain films on the corneal epithelium which are homogeneous, stable, perfectly transparent, and which adhere well, guaranteeing prolonged bioavailability of the drug, thereby forming excellent preparations with a retard effect."

(This retard effect is specifically taught in Balazs, United States Patent 4,141,973.) This is repeated elsewhere in a patent such as at column 2, lines 44-51. What is not discussed is the fact that when applied to the skin (dermatologically) these dosages would "dry up and flake off".

10. In my opinion Della Valle does not add anything different to the knowledge of persons skilled in the art in this regard. Persons skilled in the art would not use the teachings of Della Valle (or any of the prior art) to prepare dermatological preparations using hyaluronic acid (without other ingredients that were needed to cause penetration) because the hyaluronic acid would be expected to dry up and flake off.

11. While Della Valle discusses quantitative ratios by weight and concentrations (at columns 8 and 9) of the two components extending over a vast ratio range, this does not mean that Della Valle appreciated the benefits of Applicants' invention. The quantitative ratio and concentrations at columns 8 and 9 respectively are, because of the large range, meaningless and unrealistic. The ratio of concentrations of between 0.01% to 75% means a 7,500 fold variation (75:.01). Extensive experimentation would be required from reading Della Valle to be undertaken to "discover" what concentrations and effective amounts could be used for what diseases or conditions. It is as if Della Valle claimed hyaluronan together with a chemical, nothing more.

12. In my experience the eye is substantially different from the skin. I would not have used the teachings of Della Valle to make dermatological preparations of any concentrations. In 1989 I thought (and persons skilled in the art thought) that hyaluronan was so hydrophilic that it would dry up and flake off and there would be no benefit to the skin. Therefore, despite the purported teachings of Della Valle with respect to uses in other areas such as dermatologically I, and persons skilled in the art, would have believed that there would have been no benefit of applying hyaluronic acid to the skin containing medication (in any concentrations) because the composition dosage amount would have to remain on the skin for a long time to permit the skin to absorb the medicine therefrom by which time the hyaluronic acid would have dried up and flaked off. Even to the present date persons skilled in the art do not generally know the characteristics of hyaluronic acid.

13. Thus, there would be no motivation from the words of Della Valle to prepare dermatological preparations because persons skilled in the art would believe that any dosages prepared would not be useful (they would, when applied, dry up and flake off and not be expected to permit the dosage amount of the medicine to be absorbed or be washed away if applied to mucous membranes) and such persons skilled in the art would have to "invent" Applicants' invention (its unique uses arising from the unique concentrations and combinations).

14. I have had in excess of 20 years experience in this area and I must say I am very surprised by the Examiner's conclusions. There is no evidence in the literature that I am aware of prior to 1989 that permits her to arrive at her conclusions. I have read the Della Valle reference referred to by the Examiner and the reference does not teach either singly or in combination with the knowledge of persons skilled in the art, the claimed compositions and methods

of treatment using those dosages as claimed in the response. Della Valle purports to teach ranges of concentrations which are meaningless. Examples are given but are outside of Applicants' concentrations and, in any event, use reaction products of hyaluronan and a basic medicine. Applicants' compositions provide novel compositions with unexpected utility - they are used to treat the diseases and conditions set out in the application.

15. Additionally, Applicants' claimed dosages would not exist but for the fact of Applicants' unique methods of treatment because there would be no other reason to make them. There is no motivation in Della Valle to develop the methods of treatment as taught by Applicants; nor is there any motivation or any teaching to arrive at the dermatological preparations (compositions and dosages) as claimed in the present application. Furthermore, the pharmaceutical compositions comprising forms of hyaluronic acid in the concentrations and in the molecular weight range given, together with an agent (also in the concentrations given) which is suitable for use to treat diseases listed in this application, is not taught.

16. These compositions and dosages give unexpected utility and are, in my opinion, not obvious. There is no teaching of Applicants' methods of treatment and Applicants' dermatological preparations in the prior art.

17. In view of the unique dosage combination containing a form of hyaluronic acid having a molecular weight less than 750,000 daltons and an effective amount of the medicinal and/or therapeutic agent which combination is used to treat the disease listed in Applicants' application the unexpected properties of the dosages and the unexpected treatment resulting from using the dosages provides unexpected benefits to the patient. There is no teaching of the dosages and treatments in the prior art nor any motivation in the prior art to

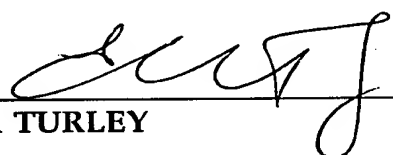
8

make these dosages for any treatments. There is no teaching anywhere of these dosages and the unexpected benefits provided by those dosages. Nor is there any teaching of the compositions which, because of their concentrations, provide the unique benefits (successful treatment of the diseases and conditions). In my opinion, the invention provides unique and totally unexpected benefits over the prior art.

18. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 20 day

of June, 1997



EVA TURLEY